

REMARKS

Claims 1, 3, 4 and 9-14 are pending in this application. Claims 11-14 have been withdrawn from consideration. By this Amendment, claims 1, 3, 4 and 9-14 have been amended. Support for the amendments to claims 1, 3, 4 and 9-14 can be found, for example, in the specification as filed at page 6, line 1. No new matter has been added.

Entry of the amendments is proper under 37 CFR §1.116 because the amendments: (a) place the application in condition for allowance (for the reasons discussed herein); (b) do not raise any new issue requiring further search and/or consideration (as the amendments amplify issues previously discussed throughout prosecution); (c) do not present any additional claims without canceling a corresponding number of finally rejected claims; and (d) place the application in better form for appeal, should an appeal be necessary. The amendments are necessary and were not earlier presented because they are made in response to arguments raised in the final rejection, and they more clearly differentiate the present claims over the cited references. Entry of the amendments is thus respectfully requested.

I. Rejection Under 35 U.S.C. §103(a)

The Office Action rejects claims 1, 3, 4, 9 and 10 under 35 U.S.C. §103(a) as allegedly being obvious over U.S. Patent Application Publication No. 2002/0115622 ("Kumagai") in view of "Preparation and Rectal Absorption of Highly Concentrated Glycyrrhizin Solution", Biol. Pharm. Bull., 2003, 26(9) p. 1299-1305 ("Koga") and "Stability of Pharmaceuticals", Journal of Pharmaceutical Sciences, 1978, 67(4), p. 443-465 ("Mollica"). Applicants respectfully traverse this rejection.

A. Kumagai

The Office Action indicates that a *prima facie* case of obviousness is shown when the subject matter is encompassed by the prior art unless there is evidence indicating that a concentration or temperature is critical. The Office Action cites *In re Aller*, 220 F.2d 454,

465 (CCPA 1955), as stating that "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." See Office Action, page 7. The ruling of *In re Aller* is not applicable to the present situation, because the general condition, i.e., the glycyrrhizin concentration, of Kumagai is not the same as the concentration range recited in claims 1 and 10.

The glycyrrhizin concentration ranges described in Kumagai do not overlap those of claims 1 and 10. Kumagai describes concentrations of 2.0 mg/mL. Kumagai, paragraphs [0048-0054]. Claims 1 and 10, however, describe glycyrrhizin concentrations of 8 to 16 mg/mL. As the ranges do not overlap, a showing of criticality of range is not necessary. Instead, to support an obviousness rejection, the references would have to either specifically disclose the recited range or provide one of ordinary skill in the art with reason or rationale to have attempted the concentration ranges recited in the claims. Kumagai, whether independently or in concert with Koga and Mollica, fails to do so.

Under MPEP §2144.05(I), where the claimed ranges and prior art ranges do not overlap, as is the case with the pharmaceutical compositions of claims 1 and 10 as compared to the therapeutic agent of Kumagai, the test for determining obviousness is not whether the range is "critical" but whether the two non-overlapping ranges are "close enough that one skilled in the art would have expected them to have the same properties." Because the glycyrrhizin concentration described in Kumagai is a power of at least 4 less than the concentration recited in claims 1 and 10, the ranges are not close enough that one skilled in the art would have expected them to have the same properties.

In *Titanium Metals Corp. of America v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) "close" was defined to be a difference of 0.05% in concentration. Here, the glycyrrhizin concentrations differ by at least 400%, and can differ by up to 800%. Clearly, in the field of pharmaceutical compositions, as in claims 1 and 10 and Kumagai, concentrations

that differ by as much as 400-800% are not sufficiently "close" that one of ordinary skill in the art would have expected the respective compositions to have the same properties. Instead, the concentrations of the present claims and Kumagai are vastly different.

Furthermore, in light of such vast a difference in concentrations between the injectable pharmaceutical compositions of claims 1 and 10 and Kumagai, the non-overlapping ranges of claims 1 and 10 and Kumagai are not close enough that one skilled in the art would have expected them to have the same properties under the above test for determining obviousness. Accordingly, Applicants have properly established that Kumagai would not have rendered claims 1 and 10 obvious by establishing that the claimed ranges and Kumagai's ranges are not "close enough that one skilled in the art would have expected them to have the same properties." Because the Patent Office has failed to establish *prima facie* obviousness, Applicants are not required to provide criticality evidence. For at least this reason, Kumagai's ranges would not have rendered claims 1 and 10 obvious.

Moreover, as page 4 of the Office Action admits, Kumagai fails to disclose a composition "wherein substantially no sulfite is contained in the pharmaceutical composition," as recited by independent claims 1 and 10. Therefore, for at least this additional reason, Kumagai's ranges would not have rendered claims 1 and 10 obvious.

B. Koga

The Patent Office asserts that Koga allegedly describes that oral administration of high concentrations of glycyrrhizin will result in detectable glycyrrhizin in plasma. See Office Action, page 5. However, Koga describes that "gastrointestinal absorption of GZ is poor after oral administration", and instead focuses on rectal administration to avoid negative effects of gastric juices and various enzymes. See Koga, page 1303, right column,

lines 22-26. Because Koga does not relate to an injectable pharmaceutical composition, but rather a rectally-administered solution, Koga fails to provide any reason or rationale for one of ordinary skill in the art to have modified an injectable composition or therapeutic agent.

The Patent Office cites Koga, page 1301, right column lines 4-10, as allegedly describing that "it is an expected result that an increased concentration of glycyrrhizin remains soluble, or stable, when in the presence of increased concentration of buffer." See Office Action, page 5. This is directly contrary to the Patent Office's assertion that Koga describes that "adjustment of pH, not the presence of phosphate, . . . increases solubility." Office Action, page 8. Applicants further emphasize that Koga favors phosphate buffered formulations, and therefore fails to render obvious claims 1 and 10, which recite injectable pharmaceutical compositions comprising glycyrrhizin, cysteine and aminoacetic acid.

The Office Action's assertion is unsubstantiated because it is based on a mischaracterization of Koga's teachings. At most, Koga teaches that "increased phosphate buffer concentration improved GZ [glycyrrhizin] solubility" (emphasis added). See page 1301, right column, lines 4-10 of Koga. Koga discusses specifically the effect of phosphate buffer on glycyrrhizin solubility, but Koga fails to discuss stability of the combination recited in claim 1 (glycyrrhizin with cysteine and aminoacetic acid) or the combination recited in claim 10 (monoammonium glycyrrhizinate with cysteine hydrochloride and aminoacetic acid). In fact, Koga is silent as to the effect of any other substance (buffer or non-buffer), other than phosphate buffer, on glycyrrhizin solubility.

Therefore, Koga provides no reason or rationale for one of ordinary skill in the art to have included 3 to 6 mg/mL of cysteine and 80 to 160 mg/mL of aminoacetic acid (as recited in claim 1), or 4 to 8 mg/mL of cysteine hydrochloride and 80 to 160 mg/mL of aminoacetic acid (as recited in claim 10), in a compound containing 8 to 16 mg/mL of glycyrrhizin. Accordingly, for at least this reason, Koga could not have rendered claims 1 and 10 obvious.

Additionally, Example 1 and Table 1 of the present specification clearly disprove the Office Action's asserted theory that cysteine hydrochloride and aminoacetic acid function as buffers, and therefore it is expected that an increased concentration of glycyrrhizin over conventional concentrations would remain soluble in the presence of increased concentration of buffers over conventional concentrations. According to the Office Action's theory, the presence of cysteine hydrochloride and aminoacetic acid in the recited concentrations alone should act as a sufficient stabilizer, and thus should prevent glycyrrhizinate precipitation and cysteine degradation. However, Example 1 shows that when 2.4 or 4.0 mg/mL of sodium sulfite is added to the cysteine hydrochloride and aminoacetic acid in the claimed concentrations, glycyrrhizinate precipitation still results. Therefore, contrary to the Office Action's assertions, glycyrrhizin did not remain soluble in the presence of cysteine hydrochloride and aminoacetic acid in the recited concentrations. Accordingly, because the obviousness rejection of the present claims over Kumagai in view of Koga is premised on a flawed rationale, the Office Action fails to establish a *prima facie* case of obviousness of claims 1 and 10 over Kumagai and Koga, alone or in combination, for this further reason.

C. Mollica

Pages 5-6 of the Office Action cites Mollica only for its alleged disclosure that omitting sodium sulfite is beneficial. The Patent Office particularly alleges that "undesired 'extrachemical' reactions can occur when stabilizing excipients are added to drug formulations" (emphasis added). Specifically, Mollica describes that "sodium bisulfite can cause precipitation of the drug from the formulation." However, at most, page 449, left column, lines 2-3 of Mollica describes that "[s]odium bisulfite can cause precipitation of imipramine hydrochloride." Mollica fails to describe that sulfites cause precipitation of glycyrrhizin, and thus that substantially no sulfite should be included in a composition with glycyrrhizin, as required by claims 1 and 10.

At most, Mollica provides a reason or rationale to one of ordinary skill in the art to have omitted sodium bisulfite in a compound containing imipramine hydrochloride, but Mollica fails to provide a reason or rationale to have omitted sodium bisulfite from a compound containing glycyrrhizin. Thus, a person having ordinary skill in the art could not have modified the compounds of Kumagai, Koga and Mollica to produce the injectable pharmaceutical compositions of claims 1 and 10, because Mollica fails to describe any specific predictable effect of sulfite on glycyrrhizin, cysteine and aminoacetic acid.

Finally, while Mollica describes that sodium bisulfite can cause precipitation of imipramine hydrochloride (Mollica, page 449, left column, lines 2-3), Mollica fails to provide any information regarding the effect of sulfite on cysteine. However, as described in Example 1 and Table 1 of the specification, sodium sulfite results in the decomposition of cysteine. As Mollica fails to discuss cysteine or the negative effect of sodium sulfite on cysteine concentrations, Mollica fails to provide any reason or rationale for one of ordinary skill in the art to have attempted the compositions of claims 1 and 10, wherein substantially no sulfite is contained in the pharmaceutical compositions, for this additional reason.

Thus, the elimination of sulfites from the composition of Kumagai would not have been obvious.

D. Conclusion

Claims 1 and 10 would not have been obvious because, again, Kumagai teaches the inclusion of sulfites in the described therapeutic agent; Koga merely teaches the behavior of glycyrrhizin in the presence of phosphate buffers, but fails to provide any description of glycyrrhizin with cysteine or aminoacetic acid (or monoammonium glycyrrhizinate with cysteine hydrochloride and aminoacetic acid), as recited in claims 1 and 10; and Mollica fails to describe any relationship between sulfites and the compounds of claims 1 and 10 (only the

relationship between sulfites and other, unrelated, compounds). Thus, the injectable pharmaceutical compositions of claims 1 and 10, comprising glycyrrhizin (or monoammonium glycyrrhizinate), cysteine (or cysteine hydrochloride) and aminoacetic acid, wherein substantially no sulfite is contained in the pharmaceutical compounds, would not have been obvious over the cited references.

Therefore, Kumagai, Koga and Mollica, whether taken independently or in concert, fail to render obvious claims 1, 3, 4, 9 and 10. Accordingly, withdrawal of the rejection is respectfully requested.

II. Rejoinder Of Claims

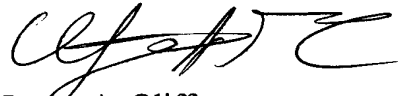
Applicants respectfully submit that claims 1, 3, 4, 9 and 10 are in a condition for allowance for at least the reasons discussed above, and therefore Applicants respectfully submit that rejoinder and consideration of withdrawn claims 11-14 is proper. MPEP §821.04 states that claims eligible for rejoinder must depend from or require all the limitations of an allowable claim. Applicants suggest that claims 11-14, drawn to methods of treating hepatic diseases or methods of treating allergy require all the limitations of independent claim 1, and therefore are eligible for rejoinder under MPEP §821.04. Accordingly, rejoinder of claims 11-14 is respectfully requested.

III. Conclusion

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of claims 1, 3, 4 and 9-14 are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

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